Cancer Research Center Hotline

Improved Methods to Stage Cancer: The Evolving Role of Sentinel Node Staging in Solid Malignancies

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Historically, one of the most controversial subjects in the management of solid malignant tumors is the impact of immediate lymphadenectomy on overall survival. Although few would argue with the importance of regional node staging, the associated morbidity has led to justifiable concern in the routine use of this procedure in cutaneous melanoma and breast cancer. Despite substantial efforts to identify primary tumor characteristics that could potentially replace the prognostic value of the status of the regional lymph nodes, in multivariate analysis, the single most powerful predictor of recurrence remains the histologic status of the regional lymph nodes. The presence of regional nodal metastases decreases 5-year survival by as much as 40%.

In the late 1980's we began studies evaluating the role of lymphatic mapping of the skin. We hypothesized that when cutaneous melanoma metastasizes via the lymphatics, it would do so to the first draining lymph node, which was termed the "sentinel" lymph node. If techniques could be developed to identify patients with metastatic disease in the sentinel node, then the majority of node negative patients could be spared an unnecessary diagnostic procedure. Initial studies in a feline model[1] demonstrate the feasibility of intraoperative lymphatic mapping and our seminal manuscript in patients with cutaneous melanoma in 1992 established the validity of the sentinel node hypothesis.[2] Current national trials are ongoing and designed to establish whether sentinel node dissection can impact survival in cutaneous melanoma[3] and breast cancer.[4]

One of the benefits of sentinel staging has been the ability to perform a focused and cost-effective examination of the regional node basin. Substantial evidence supports that when regional lymph nodes are examined in more detail either by step section and/or immunohistochemical staining, an increased number of nodes will be found to harbor metastatic disease. In certain solid malignant disease settings the findings of the "micrometastases" appears to have prognostic relevance.[5-8] However, the routine examination of a regional lymphadenectomy specimen by both step section and immunohistochemical staining is both expensive and time consuming. For this reason, it is not routinely performed in most pathology laboratories. Focusing on the regional nodes at risk for metastatic disease to define prognosis, has been a strategy that we have employed in improving staging.

Regional lymph nodes are the most common initial site for metastatic disease in most solid tumors including carcinoma of the colon and rectum. Critical decisions regarding regional and systemic therapy are dependent upon accurate staging of the regional lymphatics of colorectal cancer. Patients with Stage I or II cancer of the colon or rectum have an anticipated 5-year survival rate in excess of 75%. In contrast, individuals with N1 disease have a 5-year survival rate of only 45%-60%. The presence of nodal metastases is currently the most important factor in determining whether an individual is a candidate for adjuvant systemic therapy.

Given the potential surgical, anatomic, and pathologic variability involved in recovering lymph nodes from colorectal cancer patients, we sought to address the minimum number of nodes that needed to be examined to accurately reflect the histology of the entire node basin. Our report of 242 patients with colorectal cancer[9] validates that a minimal number of nodes need to be harvested and/or examined to accurately stage the regional lymphatics in carcinoma of the colon and rectum and establishes quality control measures that should be instituted to accurately stage this disease. Additionally, we demonstrated that routinely performing a meticulous gross examination of the resected specimen achieves nodal harvesting numbers that are equivalent to more specialized techniques to isolated lymph nodes.

The impact of inadequate nodal staging is not insignificant. The time to relapse and survival was significantly impacted by the number of nodes examined in node-negative individuals with rectal cancer indicating the heterogeneous nature of this population of patients.[10] All of these patients were treated with systemic chemotherapy and pelvic irradiation, not a clearly established standard for node negative colon cancer, suggesting that the impact on survival of by insufficient node sampling might be even more substantial in these individuals. We have demonstrated in colorectal cancer patients that the extent of pathologic assessment of the nodal status of these patients as determined by the number of nodes examined affects disease-free survival.[11] Furthermore, it is critically important when designing clinical trials in "node negative" colorectal cancer, that patients be stratified by the number of negative nodes examined.

Recognition of the critical importance of nodal staging has led to a number of strategies to improve the detection of metastatic disease in the regional lymphatics of colorectal cancer. Two fundamental strategies have been utilized: the first is to increase the number of nodes that are examined by techniques such as fat clearance and the second is a more thorough analysis of routinely identified regional lymph nodes with more sensitive assays to detect metastatic tumor cells. Neither approach is particularly appealing because of the labor involved and excessive cost associated with both approaches.

More sensitive assays clearly can identify micrometastatic deposits of disease but the value of "microstaging" remains controversial and of uncertain clinical relevance. More recently, sentinel lymph node technology has been utilized in an effort to improve staging accuracy in colorectal cancer. We have described the role of *ex vivo* sentinel node staging.[12] Following removal of the colon or rectum, the specimen was delivered to pathology in the fresh state. Briefly, the fresh colon was incised longitudinally on the anti-mesenteric

border and in the case of rectal tumors on the anterior border opposite the mesorectum. Utilizing a tuberculin syringe, four separate submucosal injections of approximately 0.125 cc of isosulfan blue (Lymphozurin 1% in aqueous solution; Ben Venue Labs, Bedford, OH) were performed in four quadrants around the tumor. A submucosal wheal of approximately 1 cm was obtained. The injection sites were then gently massaged for approximately 2-5 minutes.

The mesentery was then examined by gently incising the overlying peritoneum at the base of the palpable tumor and at the junction of the mesentery with the colon. The mesenteric fat was bluntly separated and utilizing meticulous blunt dissection, blue lymphatic channels were identified and subsequently traced through the adipose tissue of the mesentery to a blue stained lymph node. These blue stained lymph nodes were then individually harvested and submitted for histologic examination.

To date, 110 patients with carcinoma of the colon or rectum have been examined following *ex vivo* sentinel node mapping. These patients have ranged in age from 29 to 87 years (mean 64 years). The vast majority of primary tumors were either T3 (72%) or T2 (18%). Seventy-eight percent of tumors were moderately differentiated. A mean of 30 nodes were harvested (range 5-111, 95% CI 26 to 33). Forty-five patients (41%) were found to be node positive by routine H&E analysis. A total of 2007 nodes were analyzed from these 65 H&E node negative specimens (1829 non-SLN and 278 SLN). SLN were identified in all but 3 specimens. The mean number of SLN identified was 8.1 (range 0-21). Overall, SLN metastases were identified in 9 of 278 SLNs and in only 4 of 1829 non-SLNs ($p<0.001$). Only two of 65 patients (3%) of patients had evidence of metastatic disease in non-SLN when the SLN was negative. Nine apparently node negative patients (14%) were upstaged by IHC staining of the SLN. These results lend strong support to the validity of the sentinel node hypothesis in colorectal cancer.

The identification of "occult" micrometastatic disease has raised the issue of the biologic and clinical relevance of these findings. A number of retrospective studies in melanoma[5], breast cancer[6] and colorectal cancer[7, 8] have suggested that the detection of occult micrometastases in regional lymph nodes is prognostically relevant. In colorectal cancer, this remains controversial.[13-15] It might be reasonable to presume that micrometastatic deposits of tumor cells identified in regional lymph nodes represent a metastatic phenotype that is identical to the metastatic phenotype of macrometastatic nodal involvement, and therefore, the extent of metastatic involvement may not be relevant. However, it is apparent that the metastatic tumor burden, as reflected by the number of tumor positive nodes, correlates with outcome. Patients with more tumor positive nodes have a worse prognosis than individuals with fewer tumor positive nodes. Although the number of nodes involved with metastatic tumor is directly related to the extent of metastatic disease identified, patients may have extensive nodal involvement of only a few nodes while some individuals might have multiple nodes involved with only minimal replacement of the node with metastatic disease. We sought to address whether direct measurement of tumor involvement might add to the prognostic value of regional node staging.[16]

Our results found the mean metastatic nodal tumor volume was 5.1 ± 4.99 mm^3 (range 0.05- 83,434mm^3). As was anticipated, metastatic nodal tumor volume increased with the number of involved nodes. However, there was only a weak positive correlation with number of nodes involved with metastatic disease and metastatic nodal tumor volume ($r = 0.45$). Although individuals with extensive numbers of nodes involved with metastatic tumor often times have significant tumor volumes, this was not uniformly the case.

Median follow up of the study population was 39 months (range 1-87 months). The number of nodes involved with metastatic disease significantly impacted the actuarial 5-year survival. The median survival of patients with 1-3 positive node had not been reached. In contrast those with 4 or more positive nodes had a median survival of only 23 months. Individuals with 1-3 positive nodes had a substantially better survival than individuals with 4 or more positive nodes ($p<0.001$). Furthermore, the mean number of nodes involved with metastatic disease in patients free of disease was significantly less than those who had died of disease (3.1 ± 2.5 vs. 6.7 ± 5.6, $p<0.001$).

The total nodal volume of metastatic disease correlated with prognosis. Patients with increasing volume of metastatic disease were at substantially increased risk of dying of recurrent disease ($p=0.019$). Patients dying of disease had a substantially greater nodal tumor volume at diagnosis than those who had not died of disease (3705 mm^3 $\pm$ 8077 mm^3 vs. 1783 mm^3 $\pm$ 5239 mm^3, $p=0.036$). However, by a stepwise logistic regression analysis, the total nodal volume of metastatic disease (HR 0.999, 95% CI 0.999 to 0.999) did not, independent of positive nodes (HR 1.41, 95% CI 1.17 to 1.70) or number of positive (HR 1.50, 95% CI 1.22 to1.86) nodes, predict outcome.

Twelve of 62 patients with 1-3 positive nodes had only micrometastatic involvement of the regional lymph nodes (<0.2mm in diameter). There was no difference in survival between those with micrometastatic volume disease involvement and macrometastatic volume disease involvement ($p = 0.79$). Only two patients with 4 or more positive nodes had nodal volume that was micrometastatic. In order to address whether metastatic disease volume might impact survival, we stratified patients with 4 or more positive nodes based upon median volume of metastatic involvement. Again there was no difference in survival between those with high metastatic nodal volume and low metastatic nodal volume ($p=0.56$). These findings suggest that micrometastatic disease is biologically relevant.

At this time, these approaches remain investigational and are not likely to be routinely applied to the colorectal cancer patient in the near future. Therefore, attention to oncologic surgical principles and meticulous examination of the regional lymphatics in carcinoma of the colon and rectum remains of paramount importance. If adequate node sampling is not achieved, then rigorous quality control measures should be instituted to correct this critical deficit. Improved staging can translate into improved outcomes in colorectal cancer.

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